



Europäisches Patentamt
European Patent Office
Office européen des brevets

Publication number:

0 177 893
A2

EUROPEAN PATENT APPLICATION

Application number: 85112499.0
Date of filing: 03.10.85

Int. Cl.: A 61 K 9/22, A 61 K 47/00

<p>Priority: 09.10.84 US 658965 09.10.84 US 658964</p> <p>Date of publication of application: 16.04.86 Bulletin 86/16</p> <p>Designated Contracting States: BE CH DE FR GB IT LI NL SE</p>	<p>Applicant: THE DOW CHEMICAL COMPANY, 2030 Dow Center Abbott Road P.O. Box 1967, Midland, MI 48640 (US)</p> <p>Inventor: Alderman, Daniel A., 1900 Candlestick Lane, Midland Michigan 48640 (US) Inventor: Wolford, Troy D., 2901 Ronan, Apartment 3, Midland Michigan 48640 (US)</p> <p>Representative: Sternagel, Hans-Günther, Dr. et al, Patentanwälte Dr. M. Hann Dr. H.-G. Sternagel Marburger Strasse 38, D-6300 Giessen (DE)</p>
--	--

Sustained release dosage form based on highly plasticized cellulose ether gels.

A solid sustained release dosage form, including a transdermal dosage form, is disclosed comprising a gel matrix containing HPMC and a major amount of a plasticizer therefor into which gel matrix is reversibly dispersed an active organic material, such as a pharmaceutically active agent. When the dosage form is transdermal, a non-porous covering and means for adhering the dosage form to the skin of the patient are also present.

EP 0 177 893 A2

0177893

SUSTAINED RELEASE DOSAGE FORM BASED ON
HIGHLY PLASTICIZED CELLULOSE ETHER GELS

(E-2000)

5 This invention concerns a thermoplastic matrix for the controlled or sustained release of active organic materials, especially pharmaceuticals, more particularly to a thermoplastic water-soluble matrix for the sustained release thereof.

10 The object of much research in recent years has been to provide sustained release dosage forms for various active organic materials, especially pharmaceuticals. For example, many active organic materials such as insecticides, herbicides, flavorings and the like are volatile or easily degraded in the environment in which they are employed. A sustained release form
15 for such organic materials could reduce the volatilization or degradation by releasing only small amounts of the organic material, thereby keeping the level of organic material near the optimum amount needed to be effective. Thus, large excesses of the organic material
20 do not volatilize or degrade before it performs its intended function.

Pharmaceuticals are of especial interest for sustained release applications. Most pharmaceuticals have a rather narrow therapeutic range in which they
25 are of optimum benefit. Above or below this range,

the drug is ineffective and/or is toxic. In administering a tablet or capsule of the drug, the concentration thereof in the body may at first exceed therapeutic levels. Drug concentration then gradually
5 decreases with time, until it falls below the therapeutic range. Thus, the time during which the drug is present in effective amounts may be quite short.

Sustained release or controlled release dosage forms are of interest because they can deliver
10 and maintain optimum therapeutic levels of a medicament for a longer period of time than a conventional dosage form. In addition, such dosage forms can often deliver the medicament without an initial release of a greater than a therapeutic amount thereof. An additional
15 advantage is that by using a sustained release form, it is often possible to increase the time between successive administrations of the medicament, in effect reducing the frequency of administration.

Various sustained release dosage forms have
20 been developed using cellulose ethers as a release controlling component. U.S. Patent No. 3,065,142 teaches the preparation of a compressed matrix from a mixture of a powder methylcellulose or hydroxypropyl methylcellulose and an active medicament. Similar
25 technology is also disclosed in U.S. Patent Nos. 4,369,172 and 4,389,393. This dosage form has found great utility as an oral dosage form, a rectal suppository or intravaginal device. Unfortunately, however, these dosage forms have some properties which
30 tend to limit their utility. For example, such dosage forms sometimes provide a high initial release of medicament which may in some instances be undesirable.

Moreover, since the matrices in these dosage forms are not thermoplastic, the shape of such dosage forms is limited to those which can be prepared by compressing powdered cellulose ethers.

5 It is also known to sustain the release of organic materials by coating the material with a water-insoluble cellulose ether such as ethylcellulose, cellulose acetate phthalate, and the like. This approach has also been found to be useful in certain
10 instances, but the coating process employed is expensive and the shape and manner of use of the product sustained release form are limited.

 European Patent Publication No. 0050480 discloses a multiple layer sustained release dosage
15 form for the delivery of prostaglandin. Such dosage form comprises outer release controlling layers of hydroxypropyl cellulose (HPC), a water-insoluble polymer such as polyvinyl acetate or cellulose acetate, and a minor amount of a plasticizer. This added release
20 controlling layer optionally, but less preferably, contains a prostaglandin. This dosage form further contains a drug storing layer comprising a water-soluble polymer such as HPC, a prostaglandin and optionally a minor amount of a plasticizer in a
25 water-insoluble polymer. In this system, the presence of a water-insoluble polymer is considered essential to provide controlled release of the prostaglandin.

 Similarly, in European Patent Publication No. 0086093 there is disclosed a three-layer pharmaceutical dosage form. This form comprises outer layers
30 of HPC and a minor amount of a plasticizer (optionally

0177893

containing prostaglandin) and a middle drug storing layer comprised of a water-insoluble polymer, a water-soluble polymer such as polyvinylpyrrolidone or HPC, plasticizer and an organic acid. In this reference, the use of a water-insoluble polymer is considered necessary in order to provide a suitable sustained release dosage form. Moreover, this dosage form requires the formation of the respective film layers followed by lamination of the layers to form the final product. In addition, this dosage form is not said to be useful as other than a prostaglandin delivery system.

Another limitation of the foregoing dosage forms is that they are not useful as internal dosage forms such as tablets, suppositories, intravaginal devices, and the like. More recently, the use of transdermal delivery systems to deliver pharmaceuticals over an extended period has been developed. Most such systems employ a membrane at the diffusion controlling layer, in conjunction with a separate drug storing layer. Although transdermal delivery systems are becoming accepted as a means to administer a drug, it would be desirable to provide a transdermal system which is simple and inexpensive to manufacture.

In view of the deficiencies of the previously known sustained release forms, it would be desirable to provide an inexpensive, easily prepared, matrix for the sustained release of organic materials and a transdermal pharmaceutical dosage form which is widely applicable to diverse modes of pharmaceutical administration.

The present invention concerns a thermoformable sustained release matrix for the prolonged release of an active organic material, which matrix comprises: (a) a thermoplastic, water-soluble gel having a water-soluble hydroxypropyl methylcellulose homogeneously dispersed in a major amount of the weight of said gel of a plasticizer for said hydroxylpropyl methylcellulose at the proportions thereof present in said gel; and (b) an effective amount of an active organic material dispersed in said gel.

Also the present invention concerns a transdermal pharmaceutical dosage form characterized in that (a) in the above described thermoformable sustained release matrix is a thermoplastic water-soluble gel matrix having a water-soluble hydroxypropyl methylcellulose homogeneously dispersed in a major amount of the weight of said gel matrix of a plasticizer for said cellulose ether; (b) in the above described thermoformable sustained release matrix is an effective amount of a pharmaceutically active agent dispersed in said gel matrix; and furthermore including (c) as a nonporous covering attached to said gel matrix such that the gel matrix is exposed only on one side; and (d) as a means for adhering the dosage form to human or animal skin such that the exposed surface of the gel matrix is in contact with the skin without exposure to the air.

The matrix provides for excellent prolonged release of the active organic material contained therein, without releasing an initial high concentration thereof. The matrix is also thermoplastic and as such is readily formed into a variety of shapes suitable for various

modes of administration, especially transdermal forms. Because the gel matrix acts as both drug reservoir and diffusion-controlling mechanism, the dosage form is more economically and simply manufactured than conventional transdermal deliver devices.

Brief Description of the Drawings

Figure 1 is a bottom view, partially in section, of a transdermal embodiment of the dosage form of this invention.

10 Figure 2 is a cross-sectional view of the embodiment of this invention illustrated in Figure 1.

15 The dosage form of this invention comprises, as one component, a thermoplastic water-soluble gel matrix comprising a water-soluble HPMC homogeneously dispersed into a major amount of a plasticizer. The gel matrix can contain a pharmaceutically active agent.

20 The HPMC used herein contains sufficient hydroxypropoxyl and methoxyl substitution to render it water-soluble. HPMC having a methoxy degree of substitution from about 0.8 to about 2.5 and a hydroxypropoxyl molar substitution from about 0.05 to about 3.0 are generally water-soluble. "Methoxy degree of substitution" (MDS) refers to the average number of methyl ether groups present per anhydroglucose unit of the cellulose molecule. "Hydroxypropoxyl molar substitution" (HPMS) refers to the average number of moles of propylene oxide which are reacted with each anhydroglucose unit of the cellulose molecule.

The molecular weight of the HPMC used herein is not especially critical as long as the HPMC forms a gel matrix with the plasticizer employed herein. However, the molecular weight of the cellulose ether does affect both the release profile of the matrix as well as its physical properties. As a general rule, the use of higher molecular weight HPMC causes the matrix to have greater physical strength and a longer release profile. Thus, it is readily seen that the molecular weight of the HPMC is a parameter which is readily manipulated by one skilled in the art to achieve a desired release profile or physical property in the product matrix.

The molecular weight of a water-soluble cellulose ether is generally expressed in terms of the viscosity at 20°C of an aqueous solution containing two percent by weight of the polymer. Suitable HPMC include those having a viscosity from about 5 to about 100,000 centipoises. To obtain a dosage form providing a relatively fast release of active organic material such as a pharmaceutical and/or moderate physical strength, a HPMC having a viscosity of about 5-15,000, preferably 100-4000 is suitable. For more prolonged release of active organic material and/or greater strength, a HPMC having a viscosity of about 15000-100,000, preferably 15,000-75,000 is suitable. It should be noted that factors other than the particular HPMC employed also effect these properties. For example, an increasing amount of plasticizers tends to reduce the physical strength of the matrix and increase the rate of release of the active organic material.

When the matrix is a pharmaceutical dosage form or transdermal dosage form to be taken internally as in a tablet, suppository or intravaginal device, or to be used in contact with the skin, the HPMC preferably is of a purity and grade suitable for consumption.

Preferred HPMC include those having a MDS from about 1.8 to 2.0 and HPMS from about 0.2 to about 0.31 such as is commonly available under the trade names Methocel[®] E Premium and Metalose[®] 60SH; those having a MDS from about 1.1 to about 1.6 and a HPMS of 0.1 to 0.3 such as are commercially available under the tradenames Methocel[®] K Premium and Metalose[®] 90SH; and those having a MDS from about 1.1 to 1.5 and a HPMS from about 0.7 to 1.0 such as are commercially available under the tradename Methocel[®] J. (Methocel products are available from The Dow Chemical Company and Metalose products are available from Shin-etsu Chemical Company, Ltd. Japan.)

The gel matrix further comprises a plasticizer for the HPMC. The plasticizer employed herein is a material which (a) reduces the softening point of the HPMC below its decomposition temperature and desirably (b) imparts more desirable physical properties to the gel matrix. A further characteristic of the plasticizer is that it is compatible with the HPMC at the relative proportions thereof present in the matrix. By "compatible" it is meant that a substantially homogeneous dispersion or solution of the HPMC in the plasticizer is made with little or no tendency for the HPMC and plasticizer to phase separate.

Preferably, the plasticizer employed herein is also a solvent for the HPMC at the elevated temperature at which the dosage form is prepared. Such plasticizer, when mixed with the HPMC above a characteristic temperature at which the HPMC becomes soluble therein, dissolves the HPMC. Upon cooling, the mixture forms a gel matrix having especially useful properties for use in a sustained release dosage form.

Suitable plasticizers include low molecular weight polyols having aliphatic hydroxyls such as ethylene glycol; propylene glycol; 1,2-butylene glycol; 2,3-butylene glycol; styrene glycol; polyethylene glycols such as diethylene glycol, triethylene glycol, tetraethylene glycol and other polyethylene glycols having a molecular weight of about 1,000 or less; polypropylene glycols of molecular weight 200 or less; glycol ethers such as monopropylene glycol monoisopropyl ether; propylene glycol monoethyl ether; ethylene glycol monoethyl ether; diethylene glycol monoethyl ether; ester-type plasticizers such as sorbitol lactate, ethyl lactate, butyl lactate, ethyl glycolate, allyl glycolate; and amines such as monoethanolamine, diethanolamine, triethanolamine, monisopropanolamine, triethylenetetramine, 2-amino-2-methyl-1,3-propanediol and the like. Of these, the low molecular weight polyethylene glycols, ethylene glycol, low molecular weight polypropylene glycols and especially propylene glycol are preferred.

The plasticizer is employed herein in an amount sufficient to render the matrix thermoformable. Typically, the plasticizer will comprise a major amount of the weight of the matrix, i.e. at least about 30 percent by weight. Preferably, the plasticizer comprises

from about 30 to 95 percent of the combined weight of plasticizer and HPMC. The amount of plasticizer present in the matrix very substantially affects its properties. A more flexible matrix is obtained when a relatively
5 high level of plasticizer, i.e. 50 to 90 percent, is present therein. The use of a lesser amount of plasticizer (i.e. 30 to 50 percent, preferably 40 to 50 percent) provides a stiffer, harder matrix.

The matrix of this invention further contains
10 at least one active organic material, such as a pharmaceutical, which is capable of being released in active form from the matrix under the conditions at which the matrix is used. Preferably, the active organic material is heat stable, i.e. capable of being heated to a
15 temperature sufficient to prepare a gel matrix from the HPMC and the plasticizer without being rendered inactive.

The active organic material may be, for example, a herbicide, insecticide, nematocide, fungicide, antimicrobial or other biocides, a medication,
20 vitamin, coloring, preservative or any other organic compound or mixture of organic compounds which is advantageously controllably released into the system to be treated therewith. As long as the active organic material can become reversibly diffused, either alone,
25 in a solution, or with the use of a compatibilizing agent, into the cellulose ether particles, its structure is not especially critical. Suitable active organic materials range from comparatively simple molecules, like carbon tetrachloride to complex
30 molecules such as vitamins.

Exemplary herbicides include, for example, alkanolamine salts of dinitro-o-sec-butylphenol, propylene glycol butyl ethers of 2-(2,4,5-trichlorophenoxy) propanolic acid, chlorinated phenoxy acetic acid and
5 salts or esters thereof, salts of 4-amino-3,5,6-dichloropicalinic acid, as well as many other commercially available herbicides.

Suitable insecticides include, for example, chlorpyrifos-[O,O-dialkyl-O-(3,5,6-trichloro-2-pyridyl)
10 phosphorothioate], fenchlorphos-[O-O-dialkyl-O-(2,4,5-trichlorophenyl] phosphorothioate) and the like.

Suitable fungicides include 1,3-dichloropropene, trichloronitromethane (chloropicrin), mixtures thereof and the like.

15 Exemplary preservatives include the phenylphenols, chlorinated phenylphenols, chlorinated phenols, cyclopentylphenols, hexamethylenetetraamine-1,3-dichloropropane salt, as well as others.

Any of the commonly employed organic flavor-
20 ants are suitably employed herein, including, for example, orange oil, lime oil, cherry oil, lemon oil, peppermint oil, spearmint oil, wintergreen oil, licorice and other spices and fruit flavors.

Suitable pharmaceutically active agents
25 include antacids, anti-inflammatory substances, coronary vasodilators, cerebral vasodilators, peripheral vasodilators, anti-infectives, psychotropics, anti-manics, stimulants, antihistamines, laxatives, decongestants, vitamins, gastrointestinal sedatives, anti-
30 diarrheal preparations, antianginal drugs, antiarrhythmics, antihypertensive drugs, vasoconstrictors, migraine

treatments, anticoagulants, antithrombotic drugs, analgesics, antipyretics, hypnotics, sedatives, anti-emetics, antinauseants, anticonvulsants, neuromuscular drugs, hyper- and hypo- glycaemic agents, thyroid and antithyroid preparations, diuretics, antispasmodics, 5 uterine relaxants, mineral and nutritional additives, antiobesity drugs, anabolic drugs, erythropoietic drugs, antiasthmatics, expectorants, cough suppressants, mucoltics, antiuricemic drugs and other drug 10 substances such as topical analgetics, local anesthetics and the like.

If an oral dosage form is contemplated, the pharmaceutically active agent is of a type which acts orally in the mouth or which can be administered orally 15 to transmit the pharmaceutically active agent in active form to the gastrointestinal tract. Similarly, if the dosage form is a suppository or intravaginal device the drug is one which acts locally or which may be transmitted in active form through the adjacent tissues. If 20 a transdermal dosage form is contemplated, and the pharmaceutical does not readily permeate the skin, typically a low molecular weight organic material in which the drug is soluble and which itself readily permeates the skin, may be employed in the gel matrix. 25 Generally, the amount thereof is chosen such that the gel matrix retains its physical integrity.

In addition to the foregoing critical components, various optional ingredients such as are conventionally used in the art, may be employed in the 30 matrix of this invention. For example, colorings, flavorings, sweeteners, fragrances, diluents, fillers, preservatives, anti-oxidants, stabilizers, lubricants,

and the like may be employed herein if desired. Also, a minor amount of additional water soluble or insoluble polymers, such as hydroxypropylcellulose, carboxymethyl-cellulose, methyl cellulose, ethylcellulose, polyvinyl pyrrolidones, and the like may optionally be used herein. When such optional polymer is used, it does not exceed about 50 percent by weight of the weight of the HPMC used herein. The use of such optional polymers is not generally required or preferred herein, but may in certain instances be useful in providing a particular rate of release of the active agent.

The matrix of this invention can be prepared by mixing together the HPMC, plasticizer and pharmaceutically active agent under conditions sufficient to homogeneously disperse the HPMC into the plasticizer.

As described hereinbefore, the preparation of the matrix is advantageously conducted at an elevated temperature. When elevated temperatures are used, it is important to select a temperature at which the active organic material such as a pharmaceutical is stable, or if a higher temperature is desired to minimize the time during which the organic material is exposed to such temperatures in order to minimize degradation thereof. Mixing is accomplished in a conventional manner using any suitable apparatus until the HPMC is homogeneously dispersed into the plasticizer.

As stated hereinbefore, a plasticizer is preferably a material in which the HPMC becomes soluble at elevated temperatures. When such a plasticizer is used, the matrix is advantageously prepared by conducting the mixing step at a temperature at which the

HPMC is soluble in the plasticizer, subject to the limitations described hereinbefore.

Following the mixing of the HPMC, plasticizer and active organic material, the resulting dispersion
5 is cooled to form a matrix into which the active organic material is reversibly dispersed.

Because of the thermoplastic nature of the matrix of this invention, it is readily thermoformed into any desirable shape for use. For example, the
10 matrix is conveniently shaped into tablets, prills, lozenges and the like for use as an oral pharmaceutical dosage form. If desired, the matrix may be shaped into prills and placed in conventional gelatin capsules. Intravaginal devices and suppositories are readily
15 formed by shaping the matrix of this invention. Diverse complexly shaped matrixes of this invention are readily prepared to meet a wide variety of functional requirements. Shaping can be effected, for example, by injection molding, compression molding, extrusion,
20 hot dipping, melt casting and like techniques.

When the transdermal form is used, attached to the gel matrix is a non-porous covering. This covering covers all sides of the gel matrix except that side which contacts the skin. The function of the
25 covering is primarily to prevent the evaporation and oxidation of the components of the gel matrix, particularly the drug and the plasticizer. The covering is also useful to facilitate handling and prevent contamination, as well as for cosmetic purposes. The
30 covering may be of any non-irritating non-porous material, but is preferably a plastic.

The gel matrix can be attached to the covering by simply pouring the softened gel matrix into the pre-shaped covering, and then cooling the gel matrix in situ. An adhesive may be employed to further secure the attachment of the gel matrix to the covering, but is not usually necessary. Alternatively, the gel matrix and non-porous covering can be co-extruded, whereby the covering and gel matrix are shaped and joined in a single operation.

The transdermal dosage form further comprises a means for adhering the dosage form to the skin of a patient, such that the exposed gel matrix surface is in contact with the patient's skin but not exposed to the air. Various well-known adhesives are suitable for this purpose, including, for example, polymeric latexes such as polymers of styrene and butadiene, acrylic polymers and the like. The adhesive means may be applied directly to the surface of the gel matrix if the adhesive does not impede the diffusion of the drug out of the gel matrix and into the skin. Application of an adhesive in this manner is preferred in that more intimate contact between the skin and the gel matrix is achieved. However, the adhesive can be applied only to a portion of the covering which also contacts the skin during use. For example, the portion of the covering adjacent to the exposed edge of the gel matrix may be extended beyond the edge of the gel matrix to form a "lip", rim, or edge which contacts the skin. The adhesive may be attached to the "lip", rim, or edge. Alternatively, the covered gel matrix may be taped onto the patient's skin using conventional adhesive or surgical tape.

Although a separate diffusion-controlling layer is not normally required in the transdermal form, in certain instances such diffusion-controlling layer may be advantageous herein. When employed, such diffusion-controlling layer is positioned over the exposed surface of the gel matrix. Such diffusion-controlling layer generally comprises a porous polymeric membrane. Any membrane material having to be useful as a drug diffusion-controlling layer can be used herein for that purpose. Polysiloxane and cellulosic membranes are examples of such membranes.

Referring to Figure 1, the transdermal dosage form 1 has a polymeric covering 3 having a cavity containing gel matrix 2. The gel matrix contains a pharmaceutically active agent. The covering 3 has a flat flanged area 5 approximately coplanar with the exposed surface of gel matrix 2. Applied to the flat flanged area 5 is an adhesive 4 for attaching the dosage form to the skin of an animal or human patient. It is noted that the dimensions of the covering 3, cavity, and flanged area 5, may vary substantially to fit the administration requirement of any drug.

Figure 2 provides a cross-sectional view of the transdermal dosage form showing the cavity in the polymeric covering 3 in which the gel matrix 2 is contained. An adhesive layer 4 is provided on flat flanged area 5 of the polymeric covering. In packaging a removable covering is advantageously positioned over adhesive layer 4 and gel matrix 2 to prevent contamination thereof.

The transdermal dosage form of this invention is useful for the delivery of a pharmaceutically active agent to a human or animal. The dosage form is used by adhering it to the skin of the patient such that the
5 exposed gel matrix is in intimate contact with the skin. Over a period of hours or even days, the drug diffuses out of the gel matrix and through the skin, due in part to the mixture present at the interface of the skin and gel matrix. The transdermal device is
10 administered until the rate of drug diffusion through the skin is no longer sufficient to maintain a therapeutic level of drug. Often, the transdermal dosage form of this invention delivers the drug at a therapeutic level for a period of 1-50, preferably 2-24,
15 more preferably 3-12 hours.

The following examples are provided to illustrate the invention but not to limit the scope thereof. All parts and percentages are by weight unless otherwise indicated.

20 Example 1

To 75 parts propylene glycol are added at ambient temperature 25 parts of HPMC. To 95 parts of this mixture are added 5 parts of riboflavin. The resulting mixture is stirred briefly and fed into a
25 Haake 3/4 inch (1.9 cm) extruder. The temperature of the extruder zones are 120°C, 125°C, 130°C and 120°C. During the movement of the mixture through the extruder, the mixture becomes more viscous as the temperature rises and the polymer goes into solution. Dissolution
30 of the HPMC into the propylene glycol occurs at about 105°C. The resulting extrudate is a flexible rope matrix of substantial strength. A one-gram section of

said extrudate is put into a dissolution apparatus and evaluated according to the standard USP test dissolution method with 0.1N HCL as the dissolution medium and at a paddle speed of 100 rpm. The rate of release of
5 riboflavin from this sample (hereinafter referred to as Sample I-A) is provided in Table I below.

Sample No. I-B is prepared in like manner, this time employing 50 parts of the HPMC and 50 parts of propylene glycol. The matrix exhibits a dissolution
10 profile as reported in Table I below.

TABLE I

<u>Elapsed Time to Release Drug</u>			
Amount of Drug		Time (Hours)	
	<u>Released (%)</u>	<u>Sample No. I-A</u>	<u>Sample No. I-B</u>
15	10	0.5	1.0
	20	1.2	2.0
	30	2.2	3.0
	40	3.1	5.0
	50	4.5	7.1
20	60	6.0	9.6
	70	8.1	13.1
	80	11.0	17.5
	90	14.8	23.7
	100	23.6	32.0

25 As can be seen from the data presented in Table I, a very prolonged, regular release of active medicament is provided with the matrix of this invention.

Example 2

In a manner similar to that described in Example 1, Sample No. II-A is prepared by mixing 75 parts by weight of propylene glycol and 25 parts by weight of an HPMC having a MDS of 0.3-1.0, a HPMS of 1.1-1.6 and a 2% aqueous solution viscosity of 5000 centipoises. To 95 parts of this mixture are added 5 parts of riboflavin. This mixture is extruded and tested as described in Example 1 with results as reported in Table II below.

Sample No. II-B is prepared in like manner, this time substituting a 20,000 centipoise HPMC for the 5000 centipoise material employed in Sample No. II-A. Similarly, Sample No. II-C is prepared, this time substituting a 40,000 centipoise HPMC for the 5000 centipoise material used in Sample No. II-A. The release profile of these samples are as described in Table II below.

TABLE II

Elapsed Time to Release Drug		Time (Hours)		
Amount of Drug Released (%)	Sample No. II-A	Sample No. II-B	Sample No. II-C	
10	0.5	0.6	0.6	
20	1.1	1.8	1.9	
30	2.1	2.8	3.7	
40	3.3	4.1	5.2	
50	4.8	5.8	7.1	
60	6.4	7.5	9.2	
70	8.2	9.5	12.1	
80	10.2	12.0	15.6	
90	12.8	15.1	19.7	
100	17.4	21.3	24.9	

As can be seen from the results in Table II, each of Sample Nos. II-A, II-B and II-C provides excellent sustained release of riboflavin. These data also illustrate the effect of molecular weight on the release profile of the dosage form. The results reported in Table II show that a more prolonged release profile is provided with the higher molecular weight HPMC.

Example 3

Sample No. III-A is prepared by adding to 40 parts of HPMC having an MDS of 1.1 to 1.6, a HPMS of 0.7-1.0 and a 2% aqueous solution viscously of 15 centipoises, 5 parts dibromonitrilopropionamide (DBNPA) dissolved in 55 parts tetraethylene glycol. These components are stirred and extruded through a Haake Rheomex extruder at 80-82°C. A flexible gel extrudate is obtained.

A 2.036 g sample of the extrudate is dissolved in sufficient water to form a 1% aqueous DBNPA solution. The solution is aged one day, at room temperature and then is incorporated into multiple nutrient agar plates at 10, 25, 50, 100, 250 and 500 ppm DBNPA. Each plate is inoculated with Bacillus subtilis, Enterobacter aerogenes, Escherichia coli, Klebsiella pneumoniae, Proteus vulgaris, Pseudomonas aeruginosa, Salmonella choleraesuis, and Staphylococcus aureus. After incubation for 24 hours at 30° and refrigeration another 48 hours the growth of the bacteria is observed. The minimum inhibiting concentration for the gel matrix is found to be slightly better than that of DBNPA delivered from a standard aqueous solution.

The experiment is repeated with Sample No. III-B, which is like Sample no. III-A except 47.5 parts each of HPMC and tetraethylene glycol are used. The minimum inhibitory concentration is generally equal to that of DBNPA delivered from a standard tetraethylene glycol solution. However, this test verifies the release of DBNPA in active form from the gel matrix.

Example 4

A gel matrix is prepared by mixing together 25 parts by weight of propylene glycol and 75 parts by weight of a HPMC having an MDS of about 1.1 to 1.6, a HPMS of about 0.7 to 1.0 and a viscosity as a 2% aqueous solution of 5 centipoises. To this mixture are added 5 parts of riboflavin. The resulting mixture is stirred briefly and fed into a Haake 3/4 inch (1.9 cm) zone extruder. The extruder zones are at 120°C, 125°C, 130°C and 120°C, respectively. During the movement of the mixture through the extruder, it becomes more viscous as the temperature rises and the polymer goes into solution. Dissolution of the HPMC into the propylene glycol occurs at about 105°C. The resulting extrudate is a flat ribbon about 1/10 inch thick and 1 inch wide (0.25 cm x 2.54 cm).

A one inch section (2.54 cm) of the gel matrix is softened and placed into the cavity of a plastic covering having a flanged edge. An adhesive is placed on the flanged edge and the covering containing the gel matrix is fastened to a lightly water-moistened paper towel to simulate the condition of transdermal drug delivery. After a few hours, leaching of the riboflavin through the moistened paper towel is seen. The leaching continues for several days, demonstrating that the drug is gradually released from the gel matrix to a moist porous substrate.

1. A thermoformable sustained release matrix for the prolonged release of an active organic material, which matrix comprises: (a) a thermoplastic water-soluble gel having a water-soluble hydroxypropyl methylcellulose homogeneously dispersed in a major amount of the weight of said gel of a plasticizer for said hydroxypropyl methylcellulose at the proportions thereof present in said gel; and (b) an effective amount of an active organic material dispersed in said gel.

2. A matrix of Claim 1 as a transdermal pharmaceutical dosage form characterized in that (a) is a thermoplastic water-soluble gel matrix having a water-soluble hydroxypropyl methylcellulose homogeneously dispersed in a major amount of the weight of said gel matrix of a plasticizer for said cellulose ether; (b) is an effective amount of a pharmaceutically active agent dispersed in said gel matrix; and furthermore including (c) as a nonporous covering attached to said gel matrix such that the gel matrix is exposed only on one side; and (d) as a means for adhering the dosage form to human or animal skin such that the exposed surface of the gel matrix is in contact with the skin without exposure to the air.

3. The matrix of Claim 1 or 2 characterized in that said plasticizer is a solvent for said cellulose at an elevated temperature.

4. The sustained release matrix of Claim 3 characterized in that said hydroxypropyl methylcellulose has a hydroxypropoxyl molar substitution from about 0.05 to 3.0 and a methoxyl degree of substitution from about 0.8 to 2.5.

5. The matrix of Claim 4 characterized in that said hydroxypropyl methylcellulose has a hydroxypropoxyl molar substitution for about 0.2 to 0.31 and a methoxyl degree of substitution from about 1.8 to 2.0.

6. The matrix of Claim 4 characterized in that said hydroxypropyl methylcellulose has a hydroxypropoxyl molar substitution for about 0.1 to 0.3 and a methoxyl degree of substitution from about 1.1 to 1.6.

7. The matrix of Claim 4 characterized in that said hydroxypropyl methylcellulose has a hydroxypropoxyl molar substitution for about 0.7 to 1.0 and a methoxyl degree of substitution from about 1.1 to 1.6.

8. The matrix of Claim 3 characterized in that said plasticizer is ethylene glycol, a low molecular weight polyethylene glycol, propylene glycol or a low molecular weight polypropylene glycol.

9. The matrix of Claim 4 characterized in that the active agent is an antimicrobial.

10. The matrix of Claim 1 which is an oral dosage unit, rectal suppository or intravaginal dosage form.

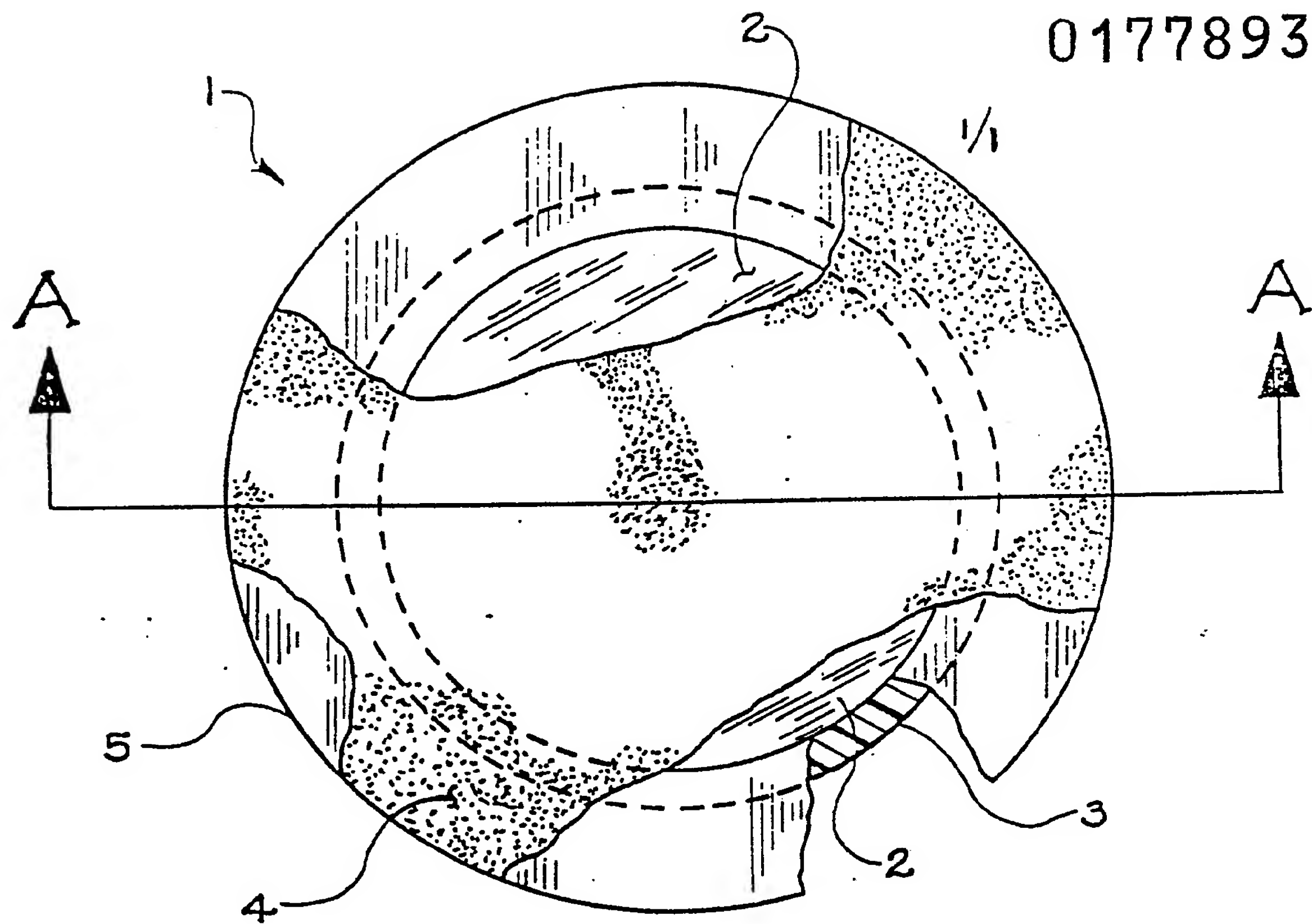
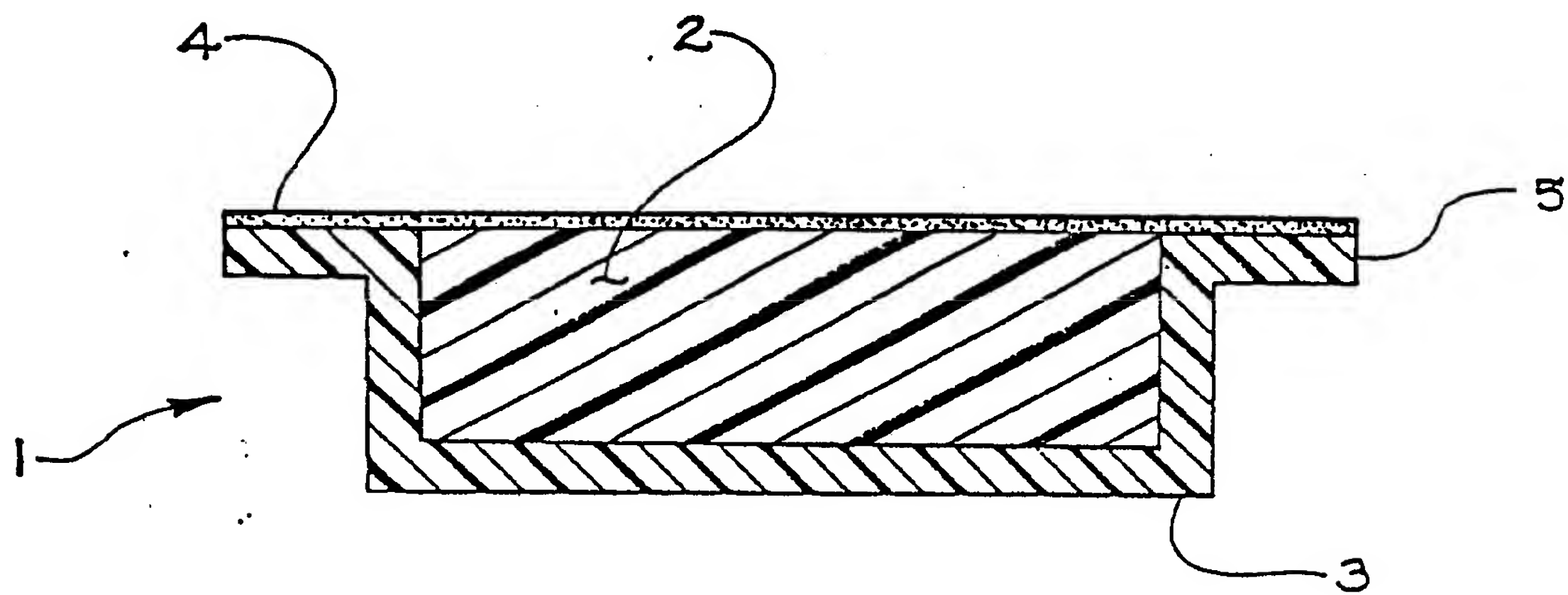


FIGURE 1



SECTION A-A

FIGURE 2